Discrete stochastic modeling of calcium channel dynamics

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We propose a simple discrete stochastic model for calcium dynamics in living cells. Specifically, the calcium concentration distribution is assumed to give rise to a set of probabilities for the opening/closing of channels which release calcium thereby changing those probabilities. We study this model in one dimension, analytically in the mean-field limit of large number of channels per site N, and numerically for small N. As the number of channels per site is increased, the transition from a non-propagating region of activity to a propagating one changes in nature from one described by directed percolation to that of deterministic depinning in a spatially discrete system. Also, for a small number of channels a propagating calcium wave can leave behind a novel fluctuation-driven state, in a parameter range where the limiting deterministic model exhibits only single pulse propagation.

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It has become clear that the intracellular nonlinear dynamics of calcium plays a crucial role in many biological processes [1]. The nonlinearity of this problem is due to the fact that there exist calcium stores inside the cell which can be released via the opening of channels which themselves have calcium-dependent kinetics. Typically, these processes are modeled using a set of coupled equations for the calcium concentration (the diffusion equation with sources and sinks) and for the relevant channels; the latter is often described by a rate equation for the fraction of open channels per unit of area. More elaborate models take into account the discrete nature of these channels, their spatial clustering, and fluctuations in the process of their opening and closing [2,3].

In this paper, we will propose and analyze a set of models which operate just with the channel dynamics alone. The justification for this is that the calcium field equilibrates quickly, with a diffusion time of perhaps 0.1s, as compared to the channel transition times, perhaps on the order of 1s for activation of a subunit to several seconds for its deactivation. One can then imagine solving for the quasi-stationary calcium concentration and thereafter using it to determine the conditional probabilities of channel opening or closing. In a subsequent paper [4], we will show how this can be done in detail starting from a specific fully-coupled model (the DeYoung-Keizer-model [5,6]); here, we will make reasonable assumptions for these probabilities and study the resulting stochastic model in a one dimensional geometry.

For specificity, we will focus on systems that have IP_3 (inositol 1,4,5- trisphosphate) channels. Each of these channels consists of a number of subunits. Here we assume that h subunits have to be activated for the channel to be open; experiments indicate that $h = 3$ [7]. A subunit is activated when IP_3 ion is bound to its corresponding domain and Ca^{2+} is bound to its activating domain and *not* bound to its inhibiting site. The characteristic time of binding and unbinding of IP_3 is typically so fast (more than 20 times faster than other binding steps [5]), that we can assume local balance of active/passive channels maintained at all times. Furthermore, we assume that the channels are spatially organized into clusters [8,9], with a fixed number of channels N per cluster and a fixed inter-cluster distance.

Our model is as follows. We introduce two stochastic variables for each channel cluster: n_i, the number of activated subunits, and m_i, the number of inhibited subunits. At every time step, the number of activated subunits n_i at site i is changed due to three stochastic processes; activation of additional subunits by binding available Ca^{2+} to their activation domains, de-activation by unbinding Ca^{2+} from active subunits, and inhibition by binding available Ca^{2+} to their inhibition domains. We take these transition rates to depend on the number of open channels at site i, c_i, and on the number of open channels at the nearest neighboring sites $i \pm 1$, $c_{i\pm1}$. Similarly, there will be binding and unbinding to the inhibitory domain, changing m_i. We denote by $p^{\pm}_{0(1)}$ the probability to activate/inhibit a subunit per number of open channels at the same site (0) or the neighboring site (1). To compute the actual probabilities, we need to multiply these by the number of open channels. Here, we use the simple expedient of taking this to equal n_i^h/hN_s^{h-1} where the total number of subunits $N_s = hN$; this is easily shown to be the expected number of open channels for large enough N. This approach allows us to avoid keeping explicit account of each of the independent subunits. Also, we let $p_d^{\pm}$ be the deactivation and deinhibition probabilities which are c independent.

Let us define the total probabilities $p^{\pm} = p_0^{\pm} + 2p_1^{\pm}$ and the "diffusion constant" $\alpha = p_1^{\pm}/(p_0^{\pm} + 2p_1^{\pm})$. We also denote $C_i(t) = (1-2\alpha)c_i(t) + \alpha c_{i-1}(t) + \alpha c_{i+1}(t)$, which mimics the amount of calcium at site i due to open channels at sites i, $i \pm 1$. Our model explicitly consists of the following coupled stochastic processes. n_i is updated

$$n_i(t + \Delta t) = n_i(t) + \Delta_n^+ - \Delta_n^- - \delta_+ \qquad (1)$$

where Δ_n^+ is a random integer number drawn from the

binomial distribution $B(\Delta_n^+, N_s - n_i(t) - m_i(t), p^+ C_i(t))$, Δ_n^- is drawn from $B(\Delta_n^-, n_i(t), p^- C_i(t))$, and δ_n^+ is drawn from $B(\delta_n^+, n_i(t), p_d^+)$. The equation for m_i reads

$$m_i(t + \Delta t) = m_i(t) + \Delta_m^+ - \delta_m^+ \qquad (2)$$

where Δ_m^+ is drawn from $B(\Delta_m^+, N_s - m_i(t), p^- C_i(t))$, and δ_m^+ is drawn from $B(\delta_m^+, m_i(t), p_d^-)$. We do not allow for transitions from the inhibited state to the activated state. In all these formulas, $B(x, y, p) \equiv \binom{y}{x} p^x (1-p)^{y-x}$. Note that the probability that IP_3 is bound is included by rescaling the number of subunits.

As a first step, we consider a simplified version of the channel dynamics with the inhibition process excluded (all p^-=0), i.e. a subunit is activated whenever Ca^{2+} is attached to its activating site. Thus we take $m_i = 0$, and arrive at the one-variable model for the number of activated subunits n_i. Let us first focus on fairly small N_s. Examples of the stochastic dynamics for several values of parameters are shown in Figure 1. At small α, an initial seed almost always ultimately dies giving rise to so-called abortive calcium waves. At larger values of α the region of activated channels typically expands at a finite rate. This transition mirrors what has been seen in many experimental systems [9].

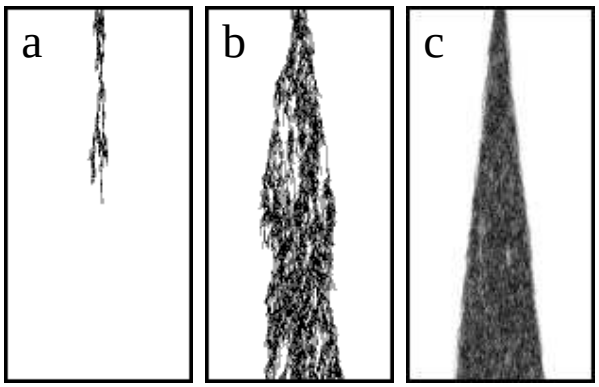

FIG. 1. Evolution of an initial seed of 5 clusters of open channels in the middle of the lattice for $p^+ N_s/h = 1$, $p_d^+ = 0.2$, $h = 3$, and $N_s = 3$, $\alpha = 0.1$ *(a)*, $N_s = 3$, $\alpha = 0.25$ *(b)*, and $N_s = 30$, $\alpha = 0.25$ *(c)*. The horizontal axis is spatial coordinate (100 sites), and the vertical axis is time (1000 iterations).

As is well known for statistical models such as the contact process [10], the critical value of α can be accurately determined by computing the distribution of survival times $\Pi(t)$ for the activation process started from a single active site. For $\alpha < \alpha_c$, the distribution falls exponentially at large t as the wave of activation eventually dies out. On the contrary, at $\alpha > \alpha_c$, $\Pi(t)$ asymptotically reaches a constant value Π_∞, since a non-zero fraction of runs produce ever-expanding active regions. At $\alpha = \alpha_c$, the distribution function exhibits a power-law asymptotic behavior with the slope determined by the universality class of the underlying stochastic process. Our data (not shown) indicate that α_c is inversely proportional to the number of subunits per site N_s. We have checked that our data is in the *directed percolation* (DP) [11] class. For example, in Fig. 2 we show $\Pi(t)$ of a cluster of open channels at the critical value of α_c for $h = 3$, $N_s = 10$ and $\gamma = 0.1$. The power-law dependence is consistent with DP prediction of $\Pi(t) \propto t^{-0.159}$. This is perhaps not too surprising. According to the Janssen-Grassberger DP conjecture [12], any spatio-temporal stochastic process with short range interactions, fluctuating active phase and unique non-fluctuating (absorbing) state, single order parameter and no additional symmetries, should belong to the DP class. This result does open up the exciting possibility that intracellular calcium dynamics could be an experimental realization of the DP process.

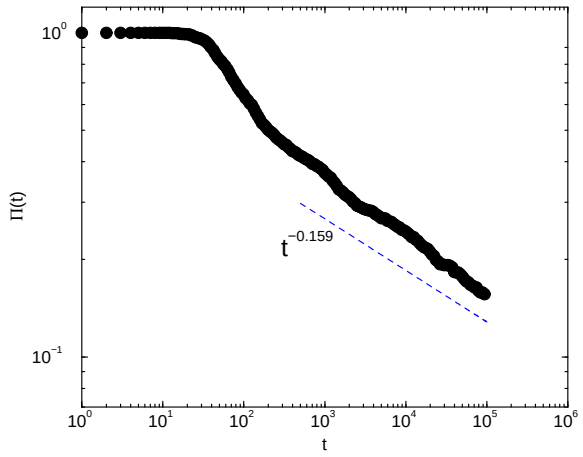

FIG. 2. The distribution of survival time for the stochastic model with $h = 3$, $\gamma = 0.1$, $N_s = 10$, and $\alpha = \alpha_c = 0.359$. Dashed line indicates the power-law scaling $\propto t^{-0.159}$.

Figure 1(c) shows the opposite limit where the dynamics becomes almost deterministic. If we take $N_s \to \infty$ and fix $pN_s/h \to P$, we can use a mean-field description in terms of the fraction of activated subunits $\rho_i = n_i/N_s$,

$$\dot{\rho_i} = ((1-2\alpha)\rho_i^h + \alpha\rho_{i-1}^h + \alpha\rho_{i+1}^h)(1-\rho_i) - \gamma\rho_i. \qquad (3)$$

and where we rescaled time $t' = Pt/\Delta t$ and introduced $\gamma = p_d/P$. For all $h \geq 2$, if $\gamma < \gamma_{cr}$ Eq.(3) the system possesses two stable uniform solutions, $\rho = 0$ and $\rho = \rho_0$ and one unstable solution ρ_u, where $\rho_{0,u}$ are real roots of the algebraic equation $\rho^{h-1}(1-\rho) = \gamma$. The front is a solution connecting these two stable fixed points; it is easy to show that this front has a unique propagation velocity.

For small α, the discreteness of our spatial lattice causes the front to become pinned, as the probability of activating subunits at the neighboring site $O(\alpha\rho_0^h)$ becomes smaller than the threshold value for excitation probability $O(\rho_u)$. The stationary front solution is described by the recurrence relation,

$$(1-2\alpha)\rho_i^h + \alpha\rho_{i-1}^h + \alpha\rho_{i+1}^h = \frac{\gamma\rho_i}{1-\rho_i} \qquad (4)$$

The bifurcation line which separates pinned and moving fronts, can be found in the limit of small α by using the ideas of ref. [13]. Indeed, in this limit, the values of ρ_i quickly (as α^i) approach 0 and ρ_0 away from the front at $i \to \pm\infty$, respectively. We can thus replace ρ_i by ρ_0 and 0 everywhere to the left and to the right of the front position except for $\rho_\pm$ at the two sites nearest to

the front, $i-1$ and $i+1$. Solving the resulting set of two algebraic equations up to α^2, one can obtain the values of $\rho_\pm$. At any γ, there is a critical value of α_m at which the real solution $\rho_\pm$ vanishes. The family of these values α_m forms the bifurcation line for front pinning in (γ, α) plane. At large α, discreteness of the mean field model (3) becomes insignificant, and (3) can be replaced by its continuum limit

$$\partial_t \rho = (\rho^h - \alpha \partial_x^2 \rho^h)(1-\rho) - \gamma\rho. \qquad (5)$$

which of course has no front pinning. Instead, α can be scaled out and there is specific value of γ at which the system goes from forward to backward propagating fronts. Figure 3 shows the phase diagram of the mean field equation (3) for $h = 3$. All the data (except possibly at the non-generic case $\gamma = 0$) are consistent with expected [13] $(\alpha - \alpha_m)^{1/2}$ scaling.

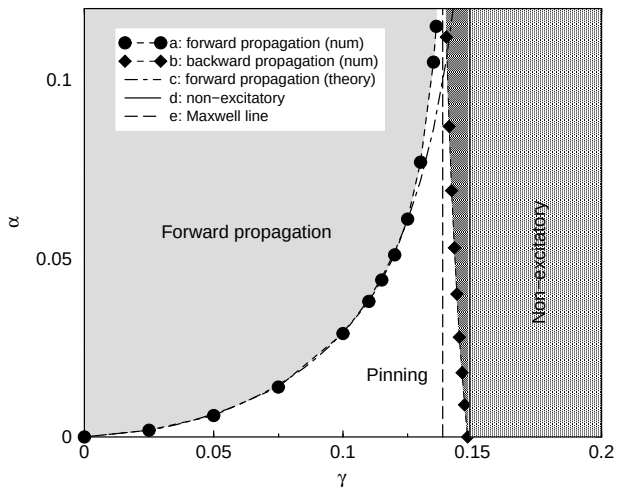

FIG. 3. Phase diagram of the mean field equation (3) for $h = 3$: *a* bifurcation line separating forward-propagating fronts from pinning region; *b* same for backward propagating fronts; *c* small-α approximation of pinning line; *d* line $\gamma = 4/27$ separating the region of non-existence of the excited state; *e* Maxwell line $\gamma = 0.138...$ separating forward and backward front propagation in the continuum limit

How does one get from DP behavior to deterministic pinning/depinning? To investigate this issue, we have performed simulations for the front speed as a function α at various finite values of N_s; with the results given in Fig. 4. At large N_s, the velocity approaches the mean field prediction as long as $\alpha > \alpha_m$. Close to critical value α_m, the velocity deviates from the mean-field dependence $V \propto (\alpha - \alpha_m)^{1/2}$ because of thermally activated "creep"; fluctuations let the front to overcome potential barriers associated with finite site separation, and lead to exponentially slow front propagation (see, e.g., [14]). Directed percolation regime is not observed at large N_s since the DP critical value α_c is less than α_m. At smaller N_s, the relative magnitude of the fluctuations grows, and the DP threshold value α_c exceeds α_m. Now, the front pinning is determined by fluctuations rather than discreteness, and the critical state exhibits the properties of directed percolation.

Now we return to the full two-variable stochastic model which describes both activation and inhibition. Since the probability of Ca^{2+} binding to the inhibition domain is typically much smaller than those for the activation domain, the inhibitor dynamics is slow. In the mean-field limit $N_s \to \infty$, this model is similar to the FitzHugh-Nagumo model often used to describe waves propagating in excitable systems. One therefore expects that for a certain range of binding/unbinding probabilities, the model gives rise to pulse propagation; that is, once the wave passes, the system goes into a state dominated by inhibition from which it slowly recovers as the inhibitory domains slowly unbind. This is indeed what we find for large enough N_s, as shown in Fig. 5(a). Behind the pair of outgoing pulses, the channels stay refractory for a certain time $O(1/p^-)$ and then return to the quiescent state.

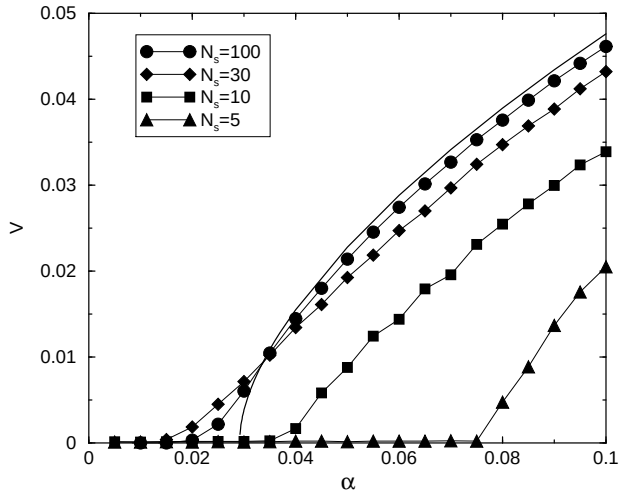

FIG. 4. The average front speed as a function of α for stochastic model at $h = 3$, $\gamma = 0.1$, $p^+ N_s/h = 1$, $p_d^+ = 0.1$, and different values of N_s. Solid line indicates the mean-field limit $N_s \to \infty$.

However, we find that having only a modest number of channels N leads to fluctuations which strongly affect the spatio-temporal behavior of the model. In fact, a new dynamical state is formed behind the outgoing fronts, a state which remains active at all subsequent times (see Fig.5,b). This state is catalyzed by backfiring, i.e. the creation of oppositely propagating waves behind a moving front. In the deterministic limit of our model, this cannot occur as the system is completely refractory once the front has passed. At finite N however, propagation of the front does not lead to the activation and subsequent inhibition of all the channels. Instead, a finite number of these remain inactivated, providing a supply of active elements that can still support wave propagation. There exist more complicated deterministic models [15], such as one proposed for CO oxidation on single crystal surfaces [16], which also appear to have pulse-induced backfiring. There, however, this effect is due to the loss of pulse stability which occurs due to the rather complex non-linear dynamics of the inhibitory field. Here, it is the fluctuations which allow for this phenomenon.

We have checked that this backfiring-induced state oc-

curs as well in more realistic and more complex models which solve for the calcium concentration together with the channel dynamics. Again, the mechanism appears to be the lack of complete inhibition in the wake of the propagating pulse. Hence, our result that one should find this behavior in intracellular calcium dynamics is not an artifact of any of the simplifying assumptions used here. Also, this state persists when the model is studied in higher dimensions. A study of the exact nature of the transition to backfiring and a comparison of the deterministic versus stochastic pathways to its existence will be undertaken in future work [4].

In summary, we proposed and studied a simple discrete model of calcium channel dynamics based on the assumption that calcium diffusion time is much smaller than the characteristic times of Ca^{2+} binding/unbinding. This model demonstrates familiar properties of deterministic reaction-diffusion systems in the limit $N \to \infty$ when fluctuations are small. For small N, we observed a transition to a directed percolation regime, in agreement with the general DP conjecture [12]. For the full model including inhibition, we found at small N a novel persistent fluctuation driven state which emerges behind a front of outgoing activation; this occurs in a parameter regime where the corresponding deterministic system exhibits only single outgoing pulses.

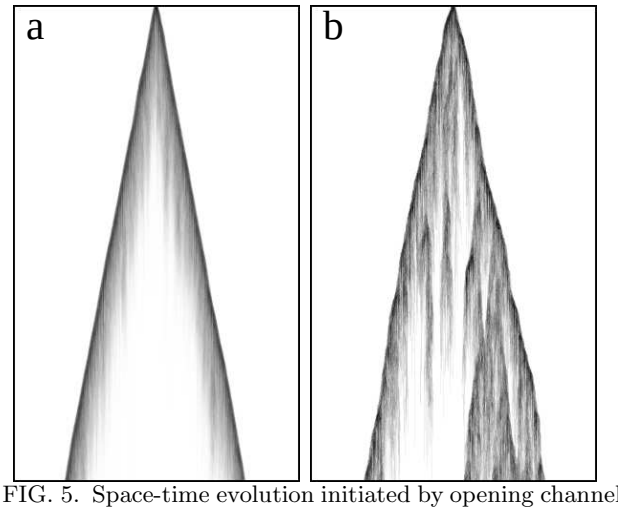

FIG. 5. Space-time evolution initiated by opening channels at a single cluster in the middle of the lattice of 300 sites for full activation/inhibition model with $p^+ = 1$, $p_d^+ = 0.04$, $p^- = 0.1$, $p_d^- = 0.12$, $h = 3$, $\alpha = 0.7$, and $N_s = 200$ (a) and $N_s = 20$ (b), 500 iterations.

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